# Clinical Reports

# Anaphylactic reaction to thiopentone: A CASE REPORT

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*A 32-year-old female was admitted for a minor elective surgical procedure. Her past history included at least six uneventful general anaesthetics. Anaphylaxis developed shortly following induction of anaesthesia with thiopentone, Innovar and gallamine. Resuscitation was successful but was complicated by ventricular fibrillation. Full recovery followed. Subsequent allergy skin tests revealed hypersensitivity to thiopentone. Recommendations for investigation of suspected hypersensitivity to anaesthetic agents are included, as are guidelines for the recognition and treatment of anaphylaxis.*

**Key words**
COMPLICATIONS: anaphylaxis, thiopentone.

The incidence of severe allergic reactions to anaesthetic agents appears to be increasing.[1] This may be due to the increasing number of general anaesthetics, the greater variety of drugs being used, cross reactions between drugs or increased reporting of such incidents.[2] In the majority of cases the reaction is unpredictable and requires immediate intervention. The mechanism of anaphylactic reaction to drugs remains unknown in large proportion of cases. Therefore investigation of such cases as to the cause and pathophysiology of anaphylaxis presents a challenge to the clinician and the immunologist.

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## Case history

A 32-year-old female was admitted to hospital for an inguinal node biopsy. She gave a four-year history of right inguinal pain following appendectomy and for several weeks prior to admission had noticed a gradual increase in swelling in the right inguinal region.

Her previous surgical history included mastoidectomy, menisectomy, appendectomy, excision of a Bartholin's abscess, laparotomy for bowel obstruction, tubal ligation and inguinal hernia repair. We confirmed that thiopentone had been given during induction for the last five of these procedures. All anaesthetic agents used prior to this admission had been well tolerated.

Apart from the surgical history the patient was in good health but was extremely anxious preoperatively. Drug history included the regular use of "Tylenol #3" (acetaminophen, caffeine, codeine) and "Percodan" (oxycodone, caffeine, acetylsalicylic acid) for the inguinal pain. She gave no history of environmental or drug allergies.

On examination, her cardiovascular and respiratory systems were normal. She was premedicated with morphine 7.5 mg and atropine 0.4 mg intramuscularly, one hour preoperatively.

On arrival in the operating room blood pressure was 140/90, pulse 88/minute and regular. The patient was induced with thiopentone, 250 mg, innovar, 0.5 ml and gallamine, 80 mg. She was then intubated, and air entry was confirmed bilaterally. There was no evidence of bronchospasm. Anaesthesia was maintained with nitrous oxide 4 l/min, oxygen 2 l/min and enflurane, with positive pressure ventilation.

Approximately eight minutes after induction the airway pressure increased and severe broncho-

spasm developed. The systolic blood pressure was 60 mmHg. The enflurane and nitrous oxide were discontinued and she was ventilated with 100 per cent oxygen. The blood pressure continued to fall. Ephedrine 50 mg and 1,000 ml of Ringer's Lactate solution was given over the next two to three minutes. The blood pressure by this time could not be recorded. The face, eyelids, hands and feet became a diffuse lobster red colour. Cyanosis developed.

The cardiac rhythm changed from sinus to ventricular fibrillation. External cardiac massage was performed immediatley. The patient received epinephrine 0.5 mg, sodium bicarbonate (7.5 per cent) 100 ml, calcium chloride 500 mg, lidocaine 75 mg, aminophylline 250 mg, and "Solucortef," 500 mg. Ringer's lactate solution was continually infused. Defibrillation with 360 J was followed by return of sinus rhythm. A dopamine infusion was started to treat the persisting hypotension and a lidocaine infusion was commenced to maintain cardiac electrical stability.

The surgical procedure was cancelled and the patient was transferred to the intensive care unit. Positive pressure ventilation and dopamine and lidocaine infusions were continued. The patient's condition improved gradually over the next 24 hours. The infusions were discontinued and the patient was extubated. Odema persisted for several days following the reaction.

One week later the patient's surgery was performed with local anaesthesia. Subsequently she was discharged home in good condition.

## Investigations

*Methods*

Allergy skin tests by the puncture (prick) method and by intradermal injections were done with serial dilutions of thiopentone (Pentothal), phenobarbitone (Luminal), pentobarbitone (Nembutal), methohexitone (Brevital), ambarbitone (Amytal), and 1:10 dilutions of pancuronium (Pavulon), droperidol (Droleptan), gallamine (Flaxedil) and fentanyl (Sublimaze).

In addition the patient received allergy prick tests with twenty inhalants (pollens, moulds, dander of animals and house dust) and twenty common foods. This was followed by ten intradermal tests with dust, pollens and moulds.

A passive transfer test (PT) was performed using the patient's husband as a recipient, after confirming that her blood was HBAg (Hepatitis B antigen) negative. In this test based on classical experiment of Prausnitz and Kustner[3] 0.1 cc of untreated patient's serum, and 0.1 cc of serum previously incubated for four hours in a 56° C water bath (to inactivate IgE antibodies) were injected intradermally into the recipient. Intradermal tests with thiopentone were done at these sites 48 hours later, with appropriate controls. The controls were a 10,000 u/ml solution of Polymixin B which releases histamine from mast cells and provides a "positive" control. A solution of buffered saline was used as "negative" control.

In the PT test in addition the recipient was tested with a solution of thiopentone in an area not pretreated with the patient's serum, to exclude the unlikely possibility that he was allergic to the drug.

Many of the drugs employed in anaesthesia, especially narcotic analgesics and muscle relaxants, have a histamine releasing property and may produce "false positive" reactions. Furthermore it was important to assure that all solutions used in skin tests are administered in concentrations not irritating to normal skin. This was accomplished experimentally by injecting serial dilutions of each drug into a volunteer.

Serum antibodies to thiopentone were sought by the ammonium sulfate coprecipitation technique using the modified method of Farr.[4]

*Results*

The skin test with thiopentone was strongly positive at a low concentration; in addition there was mild reactivity to phenobarbitone and pentobarbitone, (Table I). There was no response to tests with droperidol fentanyl, gallamine or pancuronium.

The presence of IgE antibody mediated hypersensitivity to thiopentone was confirmed by a positive passive transfer of these antibodies to the recipient (Table II). He reacted with 10/20 mm wheal/erythema to a 2 mM solution of thiopentone, and 8/15 mm to a 0.2 mM solution. A slight reaction in the site pretreated with heat inactivated serum suggests that some of the IgE antibodies escaped the

TABLE I Results of intradermal skin testing expressed in mm as measurement of wheal/erythema response

| | *Serial dilutions (concentration per 1,000 ml)* | | | | |
|---|---|---|---|---|---|
| *Testing material* | *0.002 mM* | *0.02 mM* | *0.2 mM* | *2 mM* | *10 mM* |
| Thiopentone | 5/5 | 4/10 | 10/30 | — | — |
| Phenobarbitone | — | — | — | 0/0 | 5/5 |
| Pentobarbitone | — | — | — | 0/0 | 12/30 |
| Methohexitone | — | — | — | 0/0 | 0/0 |
| Amobarbitone | — | — | — | 0/0 | 0/0 |

TABLE II Results of passive transfer test, measurement in mm wheal/erythema

| | *Passive sensitization sites* | |
|---|---|---|
| *Thiopentone mM* | *Serum untreated* | *Serum incubated 56° C/4 hrs* |
| 2.0 | 10/20 | 6/8 |
| 0.2 | 8/15 | 4/4 |

| *Skin not sensitized – control tests* | | |
|---|---|---|
| *Thiopentone 2.0 mM* | *Negative control (normal saline)* | *positive control (Polymixin B, 10,000 u/ml)* |
| 4/4 | 4/4 | 15/30 |

inactivation or, less likely, that IgG homocytotropic antibodies were present in the donor's serum.

Negative allergy tests to the forty common foods and inhalants, along with a negative personal and family history of allergy indicated that the patient was not "atopic." The coprecipitation test showed no antibodies.

## Discussion

The clinical features of profound hypotension, bronchospasm and skin rash were characteristic of an anaphylactic reaction and the time of onset suggested an anaesthetic agent as a probable cause. It was therefore mandatory to ascertain which of the agents given had been the cause, so as to avoid that agent during future procedures. It was also essential to investigate which of possible mechanisms were responsible for anaphylaxis.

Anaphylaxis may result from a number of immunologic and biochemical reactions. It may be initiated by the heat labile IgE antibody, or possibly by the less common homocytotropic variant of IgG antibody which is heat resistant, in type I immune response. The type II immune response involves classic pathway activation of the complement system. Both mechanisms involve specific antibodies, while anaphylaxis mediated by activation of alternate pathway of the complement system and anaphylactoid reactions do not involve antibodies. Type III immune reactions e.g., serum sickness, and type IV immune responses in Gell and Coombs classification[5] may produce serious clinical disorders but do not play a primary role in anaphylaxis.

Of the agents used, thiopentone and gallamine seemed the most likely cause of the reaction. Anaphylaxis to gallamine is well described in the literature,[6] affecting predominantly females.[7] Anaphylaxis to thiopentone is rare, having been estimated at about 1:30,000 administrations.[8] Most patients in whom reactions occur have a history of atopic diseases.[9] The anaphylactic reaction appears to be mediated by IgE antibodies rather than to result from a direct release of histamine by the drug.[10]

An IgE antibody mediated reaction to thiopentone as a cause of anaphylaxis in this patient is suggested by the positive allergy skin tests, and is supported further by the positive PT test. The PT test is based on a property of antibodies which cause atopic diseases (homocytotropic antibodies), to bind with mastocytes of skin. On injection into a recipient, the heat labile IgE antibodies require 24–48 hours to attain maximal skin sensitization. There may exist a small fraction of heat stable IgG homocytotropic antibodies which require a shorter incubation to sensitize skin. Their significance is uncertain.

Following incubation, the allergen is injected directly into the sensitized site. If specific for the donor's IgE antibodies, it will bind with them. Release of histamine and other biologically active substances from mastocytes will follow with formation of a "wheal and flare" which is considered a positive response (Figure).

The PT test is very specific and may be used as a diagnostic and research tool in many applications. Its main limitation is the fear that the recipient may inadvertently be infected with hepatitis or syphilis.

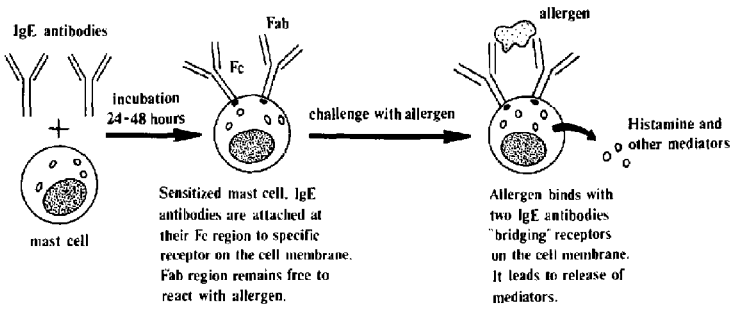


FIGURE The principle of a passive transfer test.

Furthermore some individuals may be found not suitable as recipients since their skin resists sensitization.

The antibody coprecipitation test detecting "total antibodies" specific for thiopentone and which is not selective for IgE antibodies was negative. This may be explained by the presence of only a small quantity of specific antibodies. This is not unexpected since a minute amount of IgE antibodies is sufficient to mediate an allergic reaction.

Other tests that may be used in detecting antibodies in patients reacting to anaesthetics include the radioallergosorbent test (RAST), which measures specific IgE antibodies *in vitro*. This should be a useful tool in investigating allergy to thiopentone, but it has not been developed to date for this purpose.

The leukocyte histamine release test and the IgE inhibition test may provide evidence for the presence of specific antibodies, but in view of a positive PT test these tests were not required. An extensive review of these techniques has been published recently.[11]

It is interesting to note that the patient received thiopentone for at least five previous procedures without apparent reaction. She must have become sensitized during these procedures. Though sensitization to new allergens generally occurs more readily in an atopic population, allergy to drugs may also develop with equal frequency in subjects without pre-existing allergies.[12] At the same time the atopic population may be more prone to severe and life-threatening reactions.[13]

It is of paramount importance to rapidly recognize an anaphylactic reaction and promptly institute treatment. The principles of therapy are to correct hypoxia, inhibit further release of chemical mediators and restore circulating volume.[11]

If not already intubated we believe the patient should be intubated immediately, before upper airway oedema makes this difficult or impossible. Positive pressure ventilation with 100 per cent oxygen will maximize oxygenation.

Epinephrine 5 $\mu g \cdot kg^{-1}$ should be given over two to five minutes with ECG monitoring to detect cardiac arrythmias. Large volumes of a balanced salt solution or plasma should be given to replace the massive intravascular volume loss. Aminophylline 3–5 $mg \cdot Kg^{-1}$ will reduce bronchospasm.[14] Antihistamines may block any unoccupied receptors.[11] Conticosteroids may attenuate the prolonged local and systemic effects of anaphylaxis.[15]

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## Résumé

*Une patiente de 32 ans est hospitalisée pour une intervention chirurgicale mineure. Ses antécédents nous apprennent qu'elle a eu six anesthésies antérieures sans particularité. Une réaction anaphylactique s'est développée rapidement après l'induction faite avec du thiopentone, de la gallamine et de l'innovar. La réanimation fut efficace et la patiente récupéra parfaitement malgré l'épisode de fribrillation ventriculaire qui accompagna l'incident. Des tests cutanés d'allergie ont démontré une hypersensibilité au thiopentone. Des recommandations pour l'investigation d'une hypersensibilité suspectée aux agents anesthésiques et un guide de détection et de traitement de l'anaphylaxie sont inclus.*